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EXAMINER	
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ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/851,650	BARR ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,6,8,10,12-14,16,30-34,37 and 39-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,6,8,10,12-14,16,30-34,37 and 39-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: copy of Information data sheet filed by Applicants 5/8/01

DETAILED ACTION

Application Status

1. In response to the previous Office action, a final rejection (mailed on October 21, 2003), Applicants filed an amendment (December 19, 2003) and request for continued examination (RCE) received on February 24, 2004. Said amendment has now been entered and has amended Claims 1, 3, 8, 10, 12, 30, 32, 37, 39, and 41 and cancelled Claims 2, 9, and 11. Thus, Claims 1, 3, 5, 6, 8, 10, 12-14, 16, 30-34, 37, and 39-41 are pending in the instant Office action and will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for provisional application 60/033,193 filed on December 18, 1996, non-provisional applications 08/989,332 filed in December 11, 1997 and 09/422,073 filed on October 21, 1999, and the international application PCT/US97/23014 filed on December 12, 1997.

Drawings

3. As previously noted, the drawings have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Maintained - Objections to the Specification

4. Previous objection to the specification for lacking complete continuity data in the first paragraph is maintained. Applicants have argued that claiming priority is a "right...but not a

duty" (emphasis in original). As noted in the attached copy of the application data sheet filed on May 8, 2001, priority to PCT/US97/23014 filed on December 12, 1997 has indeed been claimed as Applicants' right (see page 3). Thus, to meet the requirements for claiming this priority, that is Applicants' right, proper notation in the first paragraph of the specification is required. Appropriate amendment to the specification is required (see M.P.E.P. § 201.11).

Withdrawn – Claim Rejections - 35 U.S.C. § 112, second paragraph

5. Previous rejection of Claims 30-34, 37, 39, and 40-41(new) under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn by virtue of Applicants' amendment. Since Applicants have amended to such a specific term of art, the Examiner will clarify on the record that the term "PKS gene", as found in amended Claims 30 and 37, is art-defined as a nucleotide sequence encoding a full-length protein, i.e., a full-length open reading frame. Since PKS systems include multiple proteins with a variety of discreet domains and since the claim refers to a PKS catalytic activity, which prior to amendment would have been limited to only a domain that governs said activity, the Examiner is being clear that Claims 30 and 37 require a full-length PKS gene (open reading frame) to meet all their limitations.

6. Previous rejection of Claims 1-3, 5, 6, 10, 12-14, and 40-41 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "encodes for" is withdrawn by virtue of Applicants' amendment.

7. Previous rejection of Claims 32, 34, 37, and 39-41 under 35 U.S.C. § 112, second paragraph, as being indefinite for the requirement of the holo ACP synthase being effective in the pantetheinylation of the PKS is withdrawn by virtue of amendment to Claims 30 and 37.

8. Previous rejection of Claim 41 under 35 U.S.C. § 112, second paragraph, as being indefinite for the inclusion of "ACPS" is withdrawn by virtue of Applicant's deletion of said term.

Maintained – Claim Rejections - 35 U.S.C. § 112, second paragraph

9. Previous rejection of Claim 10 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "expression system for a cell-based detection system ... [for] a polyketide responsive target for a polyketide" is maintained. Applicants' arguments have been fully considered but are not deemed persuasive. Applicants argue that deletion of the term "functional" obviates the rejection. While the Examiner agrees the claim is clearer, the language is still confusing. By virtue of Applicants' arguments of record, it is clear that what should be encodes is a protein that will respond to the presence of a polyketide in a cell. However, the language of Claim 10 remains confusing and arduous. The Examiner suggests --- an expression system for a cell-based detection system that comprises at least one nucleotide sequence that encodes a protein that is responsive to a polyketide---. Clarification of this phrase is required.

Withdrawn – Claim Rejections - 35 U.S.C. § 112, first paragraph

10. Previous rejection of Claims 1, 2, 5, 6, 16, 32, 34, 37, and 39-41 under 35 U.S.C. § 112, first paragraph, scope of enablement, is withdrawn by virtue of Applicants' amendment to limit the instant claims to modular and/or fungal PKS expression systems.

Maintained – Claim Rejections - 35 U.S.C. § 112, first paragraph

11. Previous rejection of Claims 1, 3, 5, 6, 16, 32, 34, 37, 39, and 40 under 35 U.S.C. § 112, first paragraph, written description, is maintained. The instant rejection concerns the lack of written description for host cells or vectors containing expression systems for holo ACP synthases that pantetheinylate a PKS. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that the combination of and IUBMB category for holo ACP synthases (E.C. 2.7.8.2) and the skilled artisan's ability to assay said synthases for association with PKSs fully describes the claimed products. The Examiner disagrees. THE IUBMB category is a genus of holo ACP synthases, some of which are effective at pantetheinylating PKSs and some of which are not. While one of skill in the art would be enabled to identify appropriate holo ACP synthases using a simple screen, this screening procedure coupled with a genus of structures does not identify, by structure, the claimed sub-genus that is only holo ACP synthases effective to pantetheinylating PKSs. It is this sub-genus that must be adequately described. From the instant specification and the art, the characteristics of this subset of holo ACP synthases are unclear so that one could predict the other members of this subset. Thus, the instant rejection is maintained.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

12. Previous rejection of Claims 8, 9, 11, and 12 under 35 U.S.C. § 102(e) as being anticipated by Khosla *et al.* (USPN 5,712,146) is withdrawn by virtue of Applicant's amendment eliminating the cell-type used by Khosla *et al.*

Withdrawn - Claim Rejections - 35 U.S.C. § 103

13. Previous rejection of Claims 1-2 and 5 under 35 U.S.C. § 103(a) as being unpatentable over Lambalot *et al.* (1995) in view of Shen *et al.* (1993) is withdrawn by virtue of Applicants' amendment deleting aromatic (type II) PKSs from the claims.

14. Previous rejection of Claim 6 under 35 U.S.C. § 103(a) as being unpatentable over Lambalot *et al.* (1995) in view of Shen *et al.* (1993) and in view of Bierman *et al.* is withdrawn as noted above.

15. Previous rejection of Claims 8, 9, 11, and 12 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Bierman *et al.* is withdrawn as noted above for withdrawal of the rejection under 35 U.S.C. § 102(e).

16. Previous rejection of Claims 13 and 14 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Oliynyk *et al.* is withdrawn as noted above for withdrawal of the rejection under 35 U.S.C. § 102(e).

Maintained - Double Patenting

Previous rejection of pending claims under double patenting will be reiterated. A terminal disclaimer has been noted by Applicants previously in prosecution; however, no terminal disclaimer is pending in the instant application. In Applicant's most recent arguments, this issue was not addressed.

Statutory Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. § 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. § 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. § 101.

17. Claim 3 is rejected under 35 U.S.C. § 101 as claiming the same invention as that of claim 3 of prior U.S. Patent No. 6,033,883. This is a double patenting rejection. Both claims are drawn to *E. coli* or yeast host cells having expression systems for a PKS (6-MSAS) and a holo ACP synthase.

Non-statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

18. Claims as shown below are rejected under the judicially created doctrine of double patenting over claims as shown below of U. S. Patent No. 6,033,883 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows:

Instant application 09/851,650	U.S. Patent 6,033,883
Claims 1, 5, 6, and 40-41 are species of	Claim 1
Claims 8, 10, 12 are a species of	Claim 7
Claim 13 is a species of	Claim 18
Claim 14 is a species of	Claim 19
Claims 16 and 40-41 are species of	Claim 9
Claims 30-34 and 40-41 are genera of	Claims 27-28 and 40
Claims 37, 39, and 40-41 are species of	Claims 31 and 42

In each case, the species claimed in the instant application are disclosed within the specification of U.S. Patent 6,033,883

There is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also M.P.E.P. § 804.

19. Claims as shown below are rejected under the judicially created doctrine of double patenting over claims as shown below of U. S. Patent No. 6,258,566 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows:

Instant application 09/851,650	U.S. Patent 6,258,566
Claims 1, 3, 5, and 6 are genera of	Claims 2-5, respectively
Claims 30-34 are genera of	Claims 7-9
Claims 37 and 39 are genera of	Claims 11-12

NEW ISSUES

Objections to the Specification

20. The specification is objected to for not fully complying with the sequence rules. The amendment filed on July 28, 2003 deleted the identifier, SEQ ID NO:7, from describing the sequence disclosed on page 24, in a paragraph starting on line 17. Correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

21. Claims 1, 3, 5, 6, 8, 10, 12-14, 16, 30-34, 37, and 39-41 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 1, the abbreviations "KS" and "AT" must be defined upon their first occurrence in the claims for clarity. Moreover, the repeated definition in parentheses of "polyketide synthase (PKS)" is redundant in Claim 8,

line 7, in Claim 12, line 5, in Claim 13, line 2, in Claim 30, line 3, and in Claim 37, line 3 since it is already defined in Claim 1.

22. Claims 1, 3, 5, 6, 8, 10, 12-14, 16, and 40-41 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claims 1 and 8, the phrase "comprising...an ACP activity" is unclear since both KS and AT domains are included as "catalytic regions". Is the polypeptide region with known homology to ACP domains in PKSs intended or some other "activity". Clarification is required.

23. Claims 13-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 13, the requirement of "different" PKSs is unclear. Is this intended to include PKSs with a single amino acid change, but otherwise the same? PKSs not naturally associated with each other? PKSs from different gene cluster all together? PKSs from different organisms? Clarification is required.

24. Claims 14, 16, 30-31, 37 and 39-41 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 14, the phrase "encoding a ketoreductase (KR) activity" and similar phrases relating to DH, ER and TE activity are unclear because nucleotide sequences do not encode activities, they encode proteins having such catalytic activities. In Claims 30 and 37, the phrase "encoding a ... PKS gene" is unclear

because nucleotide sequences do not encode genes, they encode proteins. Clarification is required on both points.

25. Claims 32, 37 and 39-41 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claims 32 and 37, the phrase "expression system for a holo ACP synthase gene" is unclear since expression systems are to express proteins, not genes. Clarification is required. The Examiner suggests language like in Claim 16.

26. Claims 33 and 34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "produce a polyketide synthase activity" is unclear since the method steps are to express an encoded protein. The Examiner suggests language as found in Claim 39 for clarity.

27. Claim 40 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "derived from *Bacillus*" is unclear as to its meaning. Must the holo ACP synthase be native to Bacillus or can any holo ACP synthase, obtained from Bacillus then mutated so as to retain its activity be used? Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

28. Claims 1, 3, 5, 6, 16, 32, 34, 37, and 39-40 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for EntD, GsP, and sfp as holo ACP synthases that pantetheinylate PKSs, does not reasonably provide enablement for all holo ACP synthases that pantetheinylate PKSs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To make the claimed products to the full extent of their scope would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In the instant specification, no guidance is presented for the purpose of determining expression systems for holo ACP synthases, i.e. determining genes encoding holo ACP synthases, with no discussion of homology among the holo ACP synthases used. The specification teaches three working examples of particular holo ACP synthases, namely, EntD from *E. coli*, Gsp from *B. brevis*, and Sfp from *B. subtilis*, and demonstrate their utility as holo ACP synthases to catalyze a pantetheinyl transfer reaction which converts apo-Acps (inactive) to holo-Acps (active) in the type 1 PKS, DEBS; similar data is also found in Lambalot *et al.* (1996) (see IDS). It is noted that using a holo ACP synthase from *E. coli*, ACPS, with a type I PKS producing erythromycin, DEBS, is not operable for the production of a holo ACP of DEBS. The art involving these holo ACP synthases is not well developed, and thus, the predictability of the art is very low.

While the instant specification describes and enables means for identifying other holo ACP synthases using hybridization methods coupled to activity assays, these methods do not enable one of skill in the art to make all, or a relevant portion of, the expression systems within the scope of the claims because the ability to find a holo ACP synthase gene is not equivalent to the ability to make a holo ACP synthase gene as required by the statute (i.e., "make and use"). No description in the specification or the art provides particular residues whose encoding is important within the genus of holo ACP synthases so that its PKS pantetheinylating behavior is maintained. Thus, one of skill in the art would be unable to predict the structure of the other

members of the genus in order to make such members. Therefore, the instant claims are not enabled to the full extent of their scope.

29. Claims 8, 10, and 12-14 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for host cells that natively produce polyketides to recombinant produce polyketides in the absence of a holo ACP synthase expression system, does not reasonably provide enablement for host cells that do not natively produce polyketides to recombinant produce polyketides in the absence of a holo ACP synthase expression system. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To practice the claimed methods to the full extent of their scope would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized above.

The instant specification teaches that non-PKS, prokaryotic host cells require an additional factor, a phosphopantetheinyl transferase, such as *sfp*, as well as recombinantly expressed PKS genes to produce polyketides. The instant specification provides no guidance or working examples of making polyketides in *E. coli*, for example, without these additions. The nature of the invention is such that polyketide are complex small organic molecules with reactive groups rendering them difficult to synthesize without specific enzymes. Thus, the ability to predict how to make the host cells useful in the claimed invention to the full extent of its scope is very low. Thus, the claims are not enabled to the full extend of their scope.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

30. Claims 1, 30-34, 37, 39, and 40-41 are rejected under 35 U.S.C. § 102(e) as being anticipated by Lambalot *et al.* (USPN 6,579,695). The instant claims are drawn to *E. coli* or yeast host cells modified to contain an expression system for (1) a modular or fungal (type I) polyketide synthase, (2) a holo ACP synthase (phosphopantetheinyl transferase, specifically sfp, EntD, and/or GsP), and (3) a selectable marker. The instant claims are also drawn to methods of making the encoded PKS enzymes in the claimed host cells.

Lambalot *et al.* teach "host cells modified to express … nucleic acid encoding … phosphopantetheinyl transferase … further modified to express … nucleic acid encoding substrate of a phosphopantetheinyl transferase" as well as methods using said modified hosts to produce antibiotics, which methods incorporate methods of using the host cells to make the polyketide synthase (see column 2, lines 27-37). Lambalot *et al.* specifically teach "a host cell that has been modified to express a type I ACP and a phosphopantetheinyl transferase to activate the type I ACP" (see column 12, lines 45-47); since type I synthases "include erythromycin, rapamycin … synthases" (see column 12, lines 36-42), the disclosure of Lambalot *et al.* teaches using a full PKS enzyme. Lambalot *et al.* also teach using *E. coli*, yeast, and plant cells for their invention along with nucleic acid regulatory elements specific to each host cell system as is well-

known in the art (see column 5, lines 15-21). Lambalot *et al.* also teach using specific examples of holo ACP synthases (phosphopantetheinyl transferases) such as sfp from *B. subtilis*, EntD, and Gsp (see column 8, lines 29-47).

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

31. Claim 5 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Lambalot *et al.* (USPN 6,579,695). The instant claims are drawn to *E. coli* or yeast host cells modified to contain an expression system for (1) a modular or fungal (type I) polyketide synthase and (2) a holo ACP synthase wherein said systems are on separate vectors.

Lambalot *et al.* teach as described above. Lambalot *et al.* also teach using their invention in screening methods to discover novel antibiotics using libraries of type I polyketide synthases co-expressed with phosphopantetheinyl transferases (see column 15, lines 13-20). While Lambalot *et al.* teach separate expression vectors for phosphopantetheinyl transferases and type I PKSs (see column 13, lines 45-55), no specific reference to using two separate vectors in the methods noted in column 12 (see above) is disclosed.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to use the teachings of Lambalot *et al.* with host cells comprising phosphopantetheinyl transferases and type I PKS expression systems on separate vectors because said separate vectors

are individually taught and it would be easier to use said taught separate vectors than to combine the expression systems from said vectors into one vector. One would have had a reasonable expectation of success that said separate vectors could be incorporated into a host cell due to the extensive recombinant techniques available at the time of the invention.

32. Claims 8, 12-14, 16 and 40-41 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lambalot *et al.* (USPN 6,579,695) in view of Khosla *et al.* (USPN 5,712,146). The instant claims are drawn to *E. coli* or yeast host cells modified to contain an expression system for (1) a modular polyketide synthase and (2) a holo ACP synthase wherein said systems wherein said modular polyketide synthase expression system is on two vectors comprising PKSs from two different sources (a hybrid PKS).

Lambalot *et al.* teach as described above. Lambalot *et al.* do not teach practicing their screening method specifically using two vectors and/or making hybrid PKSs.

Khosla *et al.* teach PKS libraries in host cells making hybrid PKS combinations (see columns 13-14) and using multiple vectors (see column 18, lines 29-35).

At the time of the invention, it would have been obvious to one of skill in the art to combine the teachings of Lambalot *et al.* and Khosla *et al.* because both teach PKS libraries for the production of novel antibiotics. One would have been motivated to combine said teachings because the techniques of Lambalot *et al.* provide greater variability in the choice of host cell so that one can use the more manageable *E. coli*, for example, and because the techniques of Khosla *et al.* provide useful descriptions of variability in use of PKSs to obtain a greater variety of produced polyketide antibiotics.

Summary of Pending Issues

33. The following is a summary of the issues pending in the instant application:

a) The specification stands objected to for lacking complete continuity data in the first paragraph.
b) The specification stands objected to for not fully complying with the sequence rules.
c) Claim 10 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "expression system for a cell-based detection system ... [for] a polyketide responsive target for a polyketide".
d) Claims 1, 3, 5, 6, 8, 10, 12-14, 16, 30-34, 37, and 39-41 stand rejected under 35 U.S.C. § 112, second paragraph, for the abbreviations "KS" and "AT".
e) Claims 1, 3, 5, 6, 8, 10, 12-14, 16, and 40-41 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "comprising...an ACP activity".
f) Claims 13-14 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for "different" PKSs.
g) Claims 14, 16, 30-31, 37 and 39-41 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "encoding a ketoreductase (KR) activity" and similar phrases.
h) Claims 32, 37 and 39-41 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "expression system for a holo ACP synthase gene".
i) Claims 33 and 34 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "produce a polyketide synthase activity".
j) Claim 40 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "derived from *Bacillus*".
k) Claims 1, 3, 5, 6, 16, 32, 34, 37, 39, and 40 stand rejected under 35 U.S.C. § 112, first paragraph, written description, for holo ACP synthases that pantetheinylate a PKS.
l) Claims 1, 3, 5, 6, 16, 32, 34, 37, and 39-40 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for EntD, GsP, and sfp as holo ACP synthases that pantetheinylate PKSs, does not reasonably provide enablement for all holo ACP synthases that pantetheinylate PKSs.
m) Claims 8, 10, and 12-14 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for host cells that natively produce polyketides to recombinant produce polyketides in the absence of a holo ACP synthase expression system, does not reasonably provide enablement for host cells that do not natively produce polyketides to recombinant produce polyketides in the absence of a holo ACP synthase expression system.

n) Claims 1, 30-34, 37, 39, and 40-41 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Lambalot *et al*. (USPN 6,579,695).
o) Claim 5 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Lambalot *et al*. (USPN 6,579,695).
p) Claims 8, 12-14, 16 and 40-41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lambalot *et al*. (USPN 6,579,695) in view of Khosla *et al*. (USPN 5,712,146).
q) Claim 3 stands rejected under 35 U.S.C. § 101 as claiming the same invention as that of claim 3 of prior U.S. Patent No. 6,033,883.
r) Claims 1, 5, 6, 8, 10, 12-14, 16, 30-34, 37, 39, and 40-41 stand rejected under the judicially created doctrine of double patenting over claims of U. S. Patent No. 6,033,883.
s) Claims 1, 3, 5, 6, 30-34, 37, and 39 stand rejected under the judicially created doctrine of double patenting over claims of U. S. Patent No. 6,258,566.

Conclusion

34. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

The instant Office action is **NON-FINAL**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kathleen M Kerr
Examiner
Art Unit 1652

April 26, 2004